# CYSTEINE METABOLISM

## *General Considerations*

Cysteine participates in an extremely complex series of metabolic reactions. Figure 5 presents a general scheme. Cysteine is incorporated into most proteins and glutathione. It is also a precursor of CoA and can be readily oxidized to cystine; however, the intracellular cysteine : cystine ratio is very high (114).

Cystine is converted to thiocystine in reaction mixtures containing $\gamma$-cystathionase (115; Figure 5; see also below), but this pathway is of minor metabolic importance. Cavallini et al (116) showed that, following administration of [$^{35}$S]cystine to rats, kidney extracts and urine contained $^{35}$S-labeled taurine, hypotaurine, thiotaurine, thiazolidine carboxylate, and cysteine sulfinate. However, interpretation of the results is complicated because the DL-form of [$^{35}$S]cystine was used and some of the labeled products may have arisen nonenzymatically during the isolation procedure. The compounds mercaptoacetate-cysteine mixed disulfide [S-(carboxymethylthio)cysteine] and 3-mercaptolactate-cysteine mixed disulfide [S-(2-hydroxy-2-carboxyethylthio)cysteine] occur naturally (117). They may

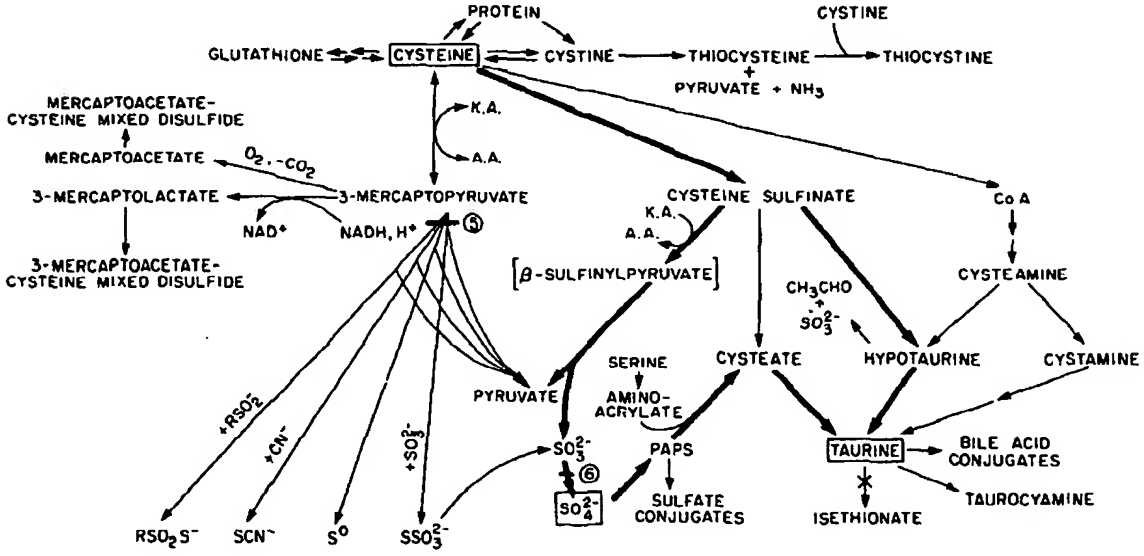



*Figure 5* Cysteine metabolism in mammals. Solid bars indicate enzymes known to be absent or modified in certain defects of man. K.A. and A.A. represent $\alpha$-keto acid substrate and amino acid product, respectively, of the cysteine and cysteine sulfinate transaminases. $\beta$-Sulfinylpyruvate is in square brackets because its existence in solution is not yet demonstrated. The relative flow of sulfur through the various pathways depends on factors such as species, sex, age, organ, and nutritional status; in general, the major flow of sulfur is through the pathways depicted with bold arrows. Sulfate and taurine are encased in order to emphasize that they are the major catabolites in urine and tissue, respectively. For more details of the interaction between thiosulfate and sulfite, see Figure 7.

arise directly from cystine (117), but are more likely formed from 3-mercaptopyruvate (Figure 5). The available evidence suggests that dietary cystine is reduced rapidly to cysteine (13) and that the major metabolic fate of cystine is conversion to cysteine (118); for a discussion of possible mechanisms for this conversion see (118).

Despite the metabolic importance of cysteine, its concentration in normal tissues is low, generally in the range of 10–100 $\mu$M (119, 120).[2] This low level may be a protection against the high reactivity of cysteine. On the other hand, the concentration of glutathione in animal tissues is much higher (0.5–10 mM) and it has long been supposed that one of the many functions of glutathione is to store cysteine (121, 122). Interestingly, glutathione levels in plasma are very low, $\sim$ 25 $\mu$M (123), but the concentration in red blood cells is much higher. Fahey et al (124) have developed a sensitive fluorescence technique for the estimation of biological thiols. In accord with earlier reports, the concentration of cysteine and glutathione in human red blood cells was found to be 8–10 $\mu$M and 2.3–2.8 mM, respectively (124).[3]

Two major pathways of cysteine breakdown in mammals are known (Figure 5), i.e. the direct oxidation (cysteine sulfinate) pathway and the transamination (3-mercaptopyruvate) pathway. However, some of the minor pathways are discussed first. Many authors still include a pathway in which cysteine is converted to pyruvate by liver "cysteine desulfhydrase" (Equation 14):

$$\text{Cysteine} + H_2O \rightarrow \text{pyruvate} + NH_3 + H_2S. \qquad 14.$$

While bacterial cysteine desulfhydrases are well characterized, no such enzyme has ever been isolated from mammalian tissues. Cavallini and co-workers (127, 128) attributed the apparent cysteine desulfhydrase activity of rat liver to $\gamma$-cystathionase. Thus, cystine present in reaction mixtures containing cysteine is converted to thiocysteine, pyruvate, and ammonia (Equation 15). If the reaction is carried out in the presence of cystine only, cysteine is produced (Equation 16):

$$\text{Cystine} + H_2O \rightarrow \text{pyruvate} + NH_3 + \text{thiocysteine}. \qquad 15.$$

$$\text{Thiocysteine} + \text{cystine} \rightarrow \text{thiocystine} + \text{cysteine}. \qquad 16.$$

[2]A compilation of concentrations of methionine, SAM, adenosylhomocysteine, cysteine, cystine, and acid soluble thiols in rat tissues has recently been published (120).

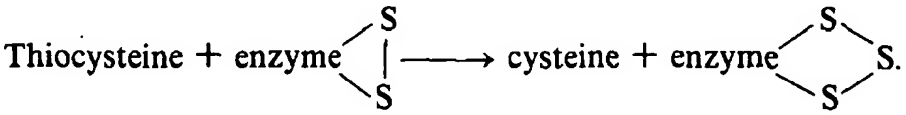
[3]The only other thiol detectable was ergothioneine (140 $\mu$M). This compound, a betaine, was first isolated from an ergot infection of rye grain in 1909 (125) and first shown to be present in human blood in 1927 (126); its origin in human blood may be due to ingested ergothioneine.

If, however, the reaction mixture contains appreciable cysteine, cystine is produced. The following reactions were thought to occur (Equations 17,18):

$$\text{Thiocysteine} \leftrightarrows \text{cysteine} + S^{\circ}. \qquad 17.$$

$$2\ \text{Cysteine} + S^{\circ} \leftrightarrows \text{cystine} + H_2S. \qquad 18.$$

Later Jollès-Bergeret & Chatagner (129) showed that γ-cystathionase catalyzes conversion of cysteine to pyruvate and ammonia even in the presence of excess 2-mercaptoethanol, i.e. under conditions in which cystine formation is negligible. These experiments suggest that rat liver γ-cystathionase catalyzes direct desulfhydration of cysteine. However, more work is needed to establish this point. More recently, Yamanishi & Tuboi (130) investigated the γ-cystathionase reaction on cyst(e)ine and showed that S° is not free in solution but is enzyme-bound as a labile sulfane (130). The following reactions were proposed:

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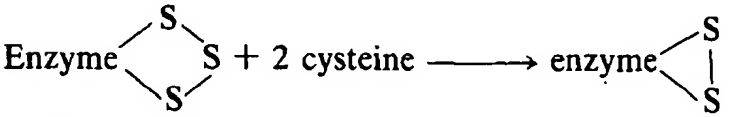


20.

$$+ S^{2-} + 2H^{+}.$$

Other –SH compounds, such as dithiothreitol, also promote removal of sulfur from the sulfane-enzyme (130). Note that both cystine and cysteine are substrates in the overall proposed reaction sequence, but cystine is regenerated. Thus, the earlier observations that mammalian organs possess a "cysteine desulfhydrase" activity is explained by the sum of reactions 15, 19, and 20 catalyzed by γ-cystathionase.

Cysteamine is present in low concentrations in rat heart (131). However, there is no evidence that cysteamine is derived by direct decarboxylation of cysteine (132). Huxtable proposed that cysteamine is derived via a complex series of reactions from CoA catabolism (133) but the pathway awaits experimental validation (132). [For recent discussion of the biochemistry of other S-containing co-factors, i.e. biotin, lipoic acid, and 8α-(S-L-cysteinyl)-riboflavin, see appropriate chapters in (15)].

Recently, Scandurra et al (134) described a pathway to cysteamine from lanthionine. The authors demonstrated that lanthionine is enzymatically degraded to aminoethylcysteine and then to cysteamine by beef kidney cortex slices (134). Lanthionine is present in acid hydrolysates of many alkali-treated proteins [see references quoted by Dowling & Maclaren (135)]; however, lanthionine is thought to arise in these preparations via nonenzymatic decomposition and cross-linking reactions with cysteine (135). Since mammalian tissues normally contain little if any free lanthionine, the pathway of lanthionine to cysteamine is probably of little metabolic importance in mammals. [Insects contain lanthionine as part of the free amino acid pool (136), but the metabolism of lanthionine in these animals has not been elucidated.]

Federici et al (137) compared cysteine oxygenase and cysteamine oxygenase activities in a number of mammalian organs and showed that optimal cysteamine oxygenase activity was at least comparable to and in many cases greater than cysteine oxygenase activity. The authors suggested that the cysteamine pathway to taurine may be more important than previously suspected (137). The product of the cysteamine oxygenase reaction (hypotaurine) is oxidized readily and nonenzymatically to taurine, but it has been difficult to demonstrate whether this reaction is also enzyme-mediated. However, hypotaurine oxidase has recently been found in various rat tissues (138) and in ox retina (139).

Many texts indicate that taurine is converted to isethionate [$(SO_3^-)CH_2$ $CH_2OH$], but careful isotope studies have been unable to detect such a pathway in mammalian organs (140). Possibly, isethionate in mammalian organs is at least in part of microbial origin (140). Interestingly, the concentrations of isethionate and taurine in the squid giant axon are remarkably high; 150 mM and $\geq$ 75 mM, respectively (141). Yet even in the squid axon, no evidence for conversion of taurine to isethionate was obtained, and the exact pathway for isethionate formation must await further study (141).

Cysteate and cystamine, in addition to hypotaurine, are potential precursors of taurine (Figure 5). Cysteate may arise by oxidation of cysteine sulfinate (probably a minor pathway) or via the PAPS transferase reaction (Figure 5). Cavallini and colleagues showed that cystamine, the disulfide of cysteamine, is a substrate of diamine oxygenase (142); the product is a cyclic imine (cystaldimine; 1,2-dehydrodithiomorpholine), which is then enzymatically cleaved by pig kidney extracts giving rise to a variety of products such as thiocysteamine, hypotaurine, thiotaurine, and taurine (143–145; Figure 6).

Equation 21 shows the sequence leading to thiocysteamine and cysteamine. Thiocysteamine and cysteamine are presumably the precursors of thiotaurine and taurine, respectively. However, thiocysteamine is unstable

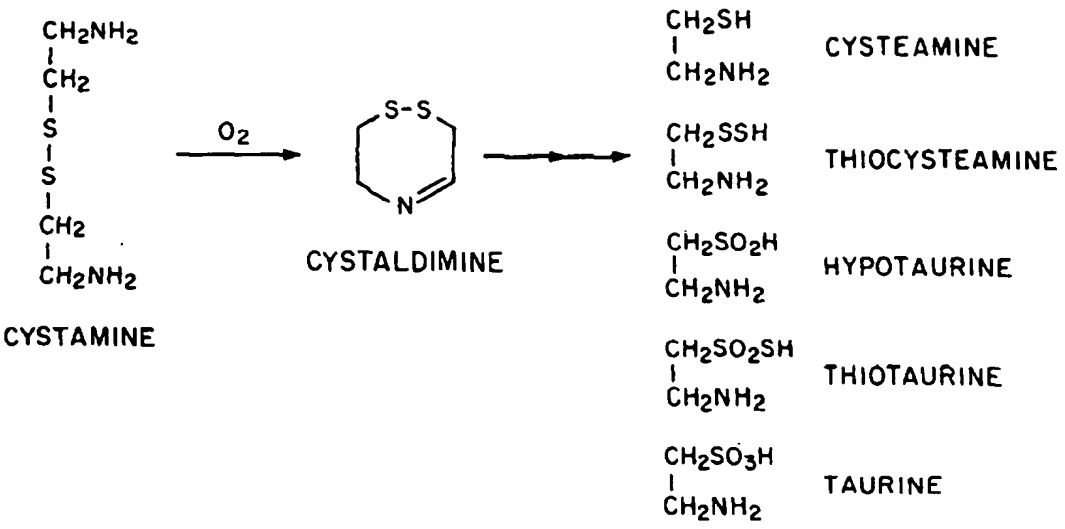


*Figure 6* Enzymatic conversions of cystamine (see 142–145).

and readily loses sulfur. Thus cystamine is readily converted to cysteamine, ammonia, a "C–2" fragment (probably glycolaldehyde or glyoxal) and labile sulfur (145). The labile sulfur is either incorporated into proteins or participates in transsulfuration reactions.

$$\text{Cystamine} \xrightarrow{NH_4^+} \text{cystaldimine} \xrightarrow{\text{"}C_2\text{"}} \text{thiocysteamine} \xrightarrow{S} \text{cysteamine.} \qquad 21.$$

Several organisms are capable of producing taurine from sulfite or sulfate via sulfation reactions leading to cysteate; for a review of this and other pathways to taurine see (146).[4] Martin and colleagues showed that $^{35}SO_4^{2-}$ in the chick could be incorporated directly into taurine without label appearing in cysteine (150). Subsequently they showed that the pathway was also present in rat liver (151). The sulfation is due to the combined action of serine dehydratase and PAPS transferase (151; Equation 22):

$$SO_4^{2-} \xrightarrow{ATP} APS \xrightarrow{ATP} PAPS \xrightarrow{\text{aminoacrylate} \leftarrow \text{serine}} \text{cysteate} + PAP \xrightarrow{O_2} \text{Taurine.} \qquad 22.$$

[4]This review also describes the occurrence and biochemistry of some unusual taurine analogs, i.e. thiotaurine, taurocyamine, hypotaurocyamine, phosphotaurocyamine, and hypophosphotaurocyamine. Taurocyamine (*N*-guanidinotaurine) was first discovered in polycheate worms (147) but was subsequently found to be a constituent of rat urine (148) and of rat tissues ($\cong 20\,\mu M$) (149). In the chick embryo yolk sac, cysteate may arise from cysteine and sulfite via a reaction catalyzed by cysteine lyase (149a).

Most texts state that cysteine is oxidized to cysteine sulfinate, which is then converted to taurine, either by (*a*) decarboxylation to hypotaurine followed by oxidation, or (*b*) oxidation to cysteate followed by decarboxylation [see appropriate chapters in (11, 14, 15, 131, 133) and Figure 5]. The enzyme activities vary widely in different tissues and from species to species, but in general, pathway (*a*) is thought to greatly predominate. Interestingly, taurine is now considered an essential amino acid for the cat (152). Some authors also regard taurine as a dietary essential amino acid for the infant but not for the human adult (153, 154).

Almost 30 years ago Kearney & Singer showed that extracts of *Proteus vulgaris* contain (*a*) a cysteine sulfinate-α-ketoglutarate transaminase activity (155), and (*b*) a cysteine sulfinate dehydrogenase activity (155a). Since this time, textbooks have shown a pathway in which β-sulfinylpyruvate is formed via transamination of cysteine sulfinate, which in turn is desulfinated to pyruvate. However, Kearney & Singer showed that desulfination was extremely rapid and nonenzymatic (155). Later, it was shown that transamination results in stoichiometric formation of sulfite (156). β-Sulfinylpyruvate has not yet been prepared. Meister suggested [discussion in (151)] that desulfination may occur when the substrate is bound at the transaminase active site and that appreciable β-sulfinylpyruvate might not be formed free in solution. Previous findings support this hypothesis: John & Fasella (158) showed that glutamate-aspartate transaminase catalyzes elimination of sulfate from L-serine-*O*-sulfate; competing transamination was much slower. At the same time, slow inactivation of enzyme occurred because of alkylation with aminoacrylate (the product of α,β-elimination) (158). Cavallini et al (159) showed that cysteine sulfinate also inactivates glutamate-aspartate transaminase and that the rate of inactivation increases in the presence of α-ketoglutarate. Presumably, in the absence of α-ketoglutarate, the enzyme catalyzes an α,β-elimination to aminacrylate and sulfite, but slow transamination to the pyridoxamine *P*-form of the enzyme results in an enzyme resistant to inactivation; the presence of α-ketoglutarate ensures turnover to the susceptible pyridoxal *P*-form of the enzyme (159). Thiosulfate protects against inactivation by both serine-*O*-sulfate and cysteine sulfinate by trapping enzyme-generated aminoacrylate with the resultant formation of alanine thiosulfonate (Equation 23; 159). Cavallini et al speculated that a role of thiosulfate may be to trap the potentially toxic aminoacrylate, generated in several enzyme-mediated reactions, as nontoxic alanine thiosulfonate (159). The naturally occurring alanine thiosulfonate may also arise via the 3-mercaptopyruvate transsulfurase reaction (see below). The PAPS reaction (Equation 22) also removes aminoacrylate.

$$XCH_2CH(NH_2)CO_2H \rightarrow CH_2{=}C(NH_2)CO_2H + XH \qquad 23.$$

$$\downarrow HSSO_3H$$

$$HO_3SSCH_2CH(NH_2)CO_2H.$$

There has been some controversy as to whether cysteine sulfinate transaminase and glutamate-aspartate transaminase are identical. Recasens & Mandel (157) purified two cysteine sulfinate transaminases from rat brain to homogeneity; both are very active with aspartate but the authors were still unable to prove whether or not their purified enzymes were the same as soluble and mitochondrial forms of glutamate-aspartate transaminase. A similar controversy ensued over whether or not brain glutamate decarboxylase and cysteine sulfinate decarboxylase are identical enzymes. However, Spears & Martin (160) recently purified three enzymes with cysteine sulfinate decarboxylase activity from pig brain; decarboxylase I and II are specific for cysteine sulfinate whereas decarboxylase III is identical to glutamate decarboxylase. Wu (161) also recently purified distinct L-cysteate/L-cysteine sulfinate and glutamate decarboxylases from bovine brain. It is also of interest that cysteine sulfinate can be converted to pyruvate and sulfite (presumably via $\beta$-sulfinylpyruvate or the corresponding $\alpha$-imino acid) in a reaction catalyzed by a dehydrogenase in *P. vulgaris* (155a).

Taurine is abundant in animal tissues; this abundance may be due in part to its relatively slow turnover (e.g. 162). Certain bacteria can catalyze transamination between taurine and $\alpha$-ketoglutarate (163), but since taurine is relatively inert in mammalian tissues, this reaction is probably of little importance in mammals. Interestingly, the taurine transaminase purified from *C. acidophila* is much more reactive with hypotaurine than with taurine (163). Recently, a mammalian hypotaurine-pyruvate ($\alpha$-ketoglutarate) transaminase was described (164). Transamination results in stoichiometric formation of acetaldehyde and sulfite (or sulfate). Evidently sulfinoacetaldehyde is extremely unstable. The possibility that desulfination occurs at the transaminase active site was also discussed (163).

## *Enzymes that Transfer Sulfane Sulfur*

Transfer reactions of bivalent, or sulfane, sulfur are catalyzed by at least three separate enzymes: rhodanese (thiosulfate thiotransferase), thiosulfate reductase, and 3-mercaptopyruvate sulfurtransferase (for review see 5, 6, 165–169). These enzymes participate in the metabolism of cysteine (and possibly cystine) and other sulfur-containing compounds of low molecular weight (5, 6, 165, 167), detoxify sulfide (170), and detoxify cyanide (165, 171). In addition, rhodanese may be responsible for restoring labile sulfur

in succinate dehydrogenase (172, 173); rhodanese and 3-mercaptopyruvate sulfurtransferase may be involved in the formation of the iron-sulfur chromophores of ferredoxin (174, 175).

RHODANESE In 1933, Lang (171) described an enzyme, which he called rhodanese,[5] that converted cyanide to the less toxic thiocyanate. Subsequently, the enzyme was purified and crystallized. The enzyme is widespread, composed of two small ($M_r$ 19,000) subunits, and possesses wide specificity (165, 176). Equation 24 summarizes the rhodanese reaction where $x = 0$, 1, or 2; A = O, H, or R; $Y^-$ = thiophilic anion; $(ASO_xS)^-$ = sulfane donor.

$$\begin{array}{ccccc} (ASO_xS)^- & \rightleftharpoons & \text{rhodanese} & \rightleftharpoons & YS^- \\ (ASO_x)^- & \rightleftharpoons & \text{rhodanese–S} & \rightleftharpoons & Y^-. \end{array} \qquad 24.$$

The reaction is of the double displacement type with the enzyme acting as a sulfur carrier (165). Szczepkowski & Wood (170) described an interesting example of a thiane transfer, which may also be of biological importance. Thus, the rhodanese reaction can be coupled to the γ-cystathionase reaction on cystine. The resultant thiocystine (Equation 16) (and possibly thiocysteine; equation 15) acts as a sulfane donor to a suitable acceptor (170; Equation 25). Thiocystine reacts more rapidly with rhodanese than does thiosulfate (170):

$$\text{Thiocystine} + Y^- \rightarrow \text{cystine} + YS^-. \qquad 25.$$

Szczepkowski & Wood suggested that the combined action of γ-cystathionase and rhodanese makes possible the efficient utilization of cystine sulfur in tissues without the appearance of sulfide ion (170).

THIOSULFATE REDUCTASE Koj and colleagues (166, 177–179) discovered this enzyme, which utilizes glutathione (Equation 26), and determined its subcellular distribution in tissues:

$$SSO_3^{2-} + 2GSH \rightarrow GSSG + H_2S + SO_3^{2-}. \qquad 26.$$

It is known that inner-labeled thiosulfate $(S \cdot {}^{35}SO_3)^{2-}$ is converted to ${}^{35}SO_4^{2-}$ more rapidly than outer-labeled thiosulfate $({}^{35}S \cdot SO_3)^{2-}$ [(178) and

[5]Lang named the enzyme rhodanese from the German word for thiocyanide, *Rhodanid*. von Euler suggested the suffix "-ese" for enzymes named for the product of the reaction. Rhodanese is the only example where this nomenclature is used. All other enzymes named for the product are referred to as synthases or synthetases.

references quoted therein]. Moreover, thiosulfate labeled in both sulfur atoms is formed when $(^{35}S \cdot SO_3)^{2-}$ is incubated with rat liver mitochondria (178). In order to explain these observations, Koj et al proposed a thiosulfate cycle (Figure 7) in which thiosulfate reductase (Equation 1; Figure 7) and rhodanese (Equation 2; Figure 7) are key enzymes (179). The cycle provides a means whereby sulfur derived from cyst(e)ine, cysteine sulfinate or 3-mercaptopyruvate is readily incorporated into sulfate.

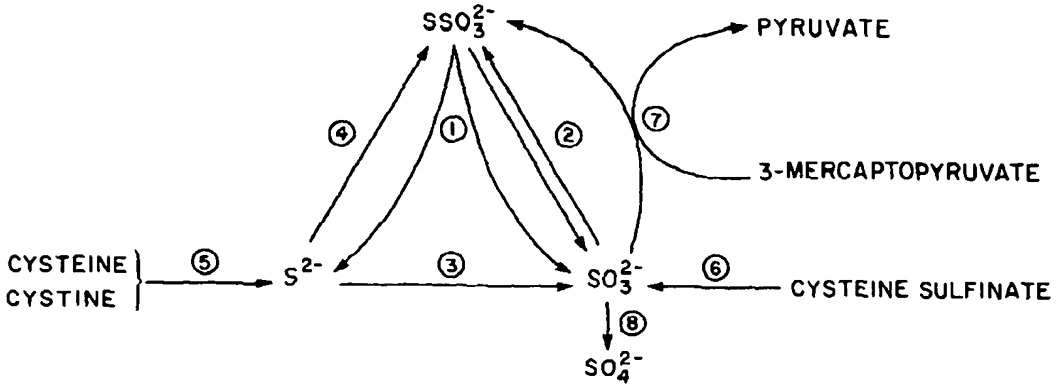


*Figure 7* Thiosulfate cycle in animal tissues: (1) Thiol-dependent reduction of thiosulfate (rhodanese or thiosulfate reductase). (2) Sulfite exchange with inner atom of thiosulfate (rhodanese). (3) Sulfide oxidation to sulfite (nonenzymatic, sulfide oxidase). (4) Sulfide oxidation to thiosulfate (nonenzymatic, sulfide oxidase). (5) Sulfide production from both cysteine and cystine in presence of γ-cystathionase. (6) Sulfite production from cysteine sulfinate (enzymatic transamination-desulfination). (7) Thiosulfate formation by sulfur transfer from 3-mercaptopyruvate to sulfite (3-mercaptopyruvate sulfurtransferase). (8) Sulfite oxidation to sulfate (sulfite oxidase). Adapted from (178); the author added enzymatic step 7.

3-MERCAPTOPYRUVATE SULFURTRANSFERASE Meister et al (180) discovered this enzyme in 1954. Attempting to demonstrate the enzymatic transamination of 3-mercaptopyruvate with a suitable amino donor, they consistently noted the appearance of alanine, rather than cysteine, on paper chromotograms. Subsequently the authors showed that rat liver possesses an enzyme that desulfurates 3-mercaptopyruvate. Elemental sulfur was shown to be the initial product; this finding was confirmed with the purified enzyme (181, 182). The enzyme is eventually inhibited by such accumulation (180, 182) but in the presence of a suitable acceptor, transsulfuration occurs (180–186). Thus, sulfur is transferred from 3-mercaptopyruvate to sulfite (183), cysteine sulfinate (183) and cyanide (184) to form thiosulfate, alanine thiosulfonate (= S-sulfocysteine) and thiocyanate, respectively. The mechanism of the transfer to cyanide has been studied in detail (182). In the presence of 2-mercaptoethanol, $H_2S$ is generated (180) but the significance of this reaction is unclear. As noted above, sulfur can also be transferred to ferredoxin. Finally, Lipsett et al (187) demonstrated an absolute

requirement for 3-mercaptopyruvate in the in vitro thiolation of *Escherichia coli* tRNA. 3-Mercaptopyruvate sulfurtransferase is widespread in animal tissues (167, 180, 188).

Compared to the cysteine sulfinate pathway, relatively little work has been carried out on the 3-mercaptopyruvate pathway. Direct evidence suggests that cysteine participates in transamination reactions (77–80, 180, 189–192). Glutamine and asparagine transaminases (78–80, 192) are capable of transaminating cysteine with a suitable donor. More recently mitochondrial cysteine-glutamate transaminase has been shown to be identical to glutamate-aspartate transaminase (189). A cysteine-glutamate transaminase not identical to glutamate-aspartate transaminase has also been described (191). The reverse reaction, conversion of 3-mercaptopyruvate to L-cysteine by transamination, has also been noted (78–80, 189–192). Cooper and Meister suggested that glutamine transaminase may act to salvage 3-mercaptopyruvate in addition to $\alpha$-keto-$\gamma$-mercaptobutyrate (79, 80, 82, 83).

Although the 3-mercaptopyruvate pathway of cysteine metabolism has received relatively little attention, strong evidence indicates it is important in vivo. Thus, [$^{35}$S]alanine thiosulfonate was detected in rat kidney and urine following administration of [$^{35}$S]cystine (116). After administration of $^{35}SO_4^{2-}$ to mutants of *A. nidulans,* Nakamura & Sato (193) noted that [$^{35}$S]alanine thiosulfonate accumulated. The authors concluded that alanine thiosulfonate is an obligatory intermediate in sulfate assimilation in these organisms. Mudd et al (194) noted that a child who eventually died with severe neurological disorders had a deficiency of sulfite oxidase (blockage 6, Figure 5) that led to the excretion of large amounts of sulfite, thiosulfate and alanine thiosulfonate. In another case, Crawhall et al described an inborn error in which large amounts of 3-mercaptolactate-cysteine-mixed disulfide were excreted in the urine (195–197). The disease was later recognized as being due to a deficiency of 3-mercaptopyruvate sulfurtransferase (blockage 5, Figure 5; 198, 199). Although in several cases the disease led to mental retardation, two sisters excreted large amounts of 3-mercaptolactate-cysteine-mixed disulfide, but were of normal intelligence (200).

## *Comments on the Metabolism of 3-Mercaptopyruvate*

Thirty years ago Meister demonstrated 3-mercaptopyruvate to be an excellent substrate of lactate dehydrogenase (201), a finding that Kun (202) subsequently verified. 3-Mercaptolactate, in the form of its mixed disulfide with cysteine, is a normal constituent of human urine (117) and is increased in the urine of patients with mercaptolactate-cysteine disulfiduria (195–197; see above). Kobayashi (117) showed that pig kidney and liver extracts can convert cystine to 3-mercaptolactate- and mercaptoacetate-cysteine mixed

disulfides. Presumably the reason for mixed disulfide formation is that thiols formed in minor amounts and oxidized in the extracellular space have a greater probability of forming a mixed disulfide with cysteine than of forming a symmetrical disulfide (167). It has been difficult to detect 3-mercaptopyruvate in biological samples because of its lability, but recently Hannestad et al (199) described a gas chromatographic method that relies on derivatization of carboxyl, thiol, and keto groups and showed that 3-mercaptopyruvate, (presumably as a mixed disulfide) is a normal trace constituent in human urine. A patient with 3-mercaptolactate-cysteine disulfiduria had a slightly elevated urine concentration of 3-mercaptopyruvate (199). Sörbo and colleagues have also developed methods for the determination of other cysteine- and 3-mercaptopyruvate-derived metabolites in urine. Interestingly, human subjects excrete $\cong$ 20–30 mmol of sulfur per day, of which at least 80% is inorganic sulfate (167, 203). Values for mercaptolactate (204), mercaptoacetate (204), *N*-acetylcysteine (204), thiosulfate (nonsmokers) (205), and thiocyanate (206) were 37, 9, 31, 32, and 44 $\mu$mol/day or $<$ 1% of total urinary sulfur.[6] Kågedal and Källenberg devised an extremely sensitive method for the detection of mercaptoacetate and *N*-acetylcysteine and report average values in normal human urine of 6.4 and 30.7 $\mu$mol/liter, respectively (210). The origin of *N*-acetylcysteine is not clear but may be related to mercapturic acid metabolism (211); presumably mercaptoacetate and its mixed disulfide arise via oxidative decarboxylation of 3-mercaptopyruvate (or its mixed disulfide with cysteine). Ubuka & Yao (212) showed that, in the absence of catalase, cystine is converted in part to mercaptoacetate-cysteine mixed disulfide by L-amino acid oxidase. It is doubtful that this reaction is responsible for the in vivo formation of mercaptoacetate; most likely the enzyme responsible is an $\alpha$-keto acid dehydrogenase . Recently, mercaptoacetate was shown to inhibit 3-hydroxybutyrate dehydrogenase (213); such an inhibition may account in part for the deleterious effects associated with sulfituria or 3-mercaptolactate-cysteine disulfiduria.

Since cyanide is extremely toxic and unlikely to arise via metabolic reactions, one might wonder about the origin of urinary thiocyanate. Cya-

[6]A portion of inorganic sulfate is activated to 3'-phosphoadenosine-5'-phosphosulfate (PAPS); sulfotransferases transfer "activated sulfate" to a large number of high and low molecular weight substrates (207; Figure 5). Thus, dermatan, keratan, heparan, and chondroitan sulfates are formed in this manner as are lipid- and polysaccharide-sulfate complexes (207). Sulfate conjugates of phenols, aliphatic alcohols, steroids, amino sugars, and choline also occur and many are found in trace amounts in the urine (208). Hypothiocyanate ($OSCN^-$) has been found in saliva (209). Apparently, hypothiocyanate and possibly higher peroxythiocyanates result from the action of lactoperoxidase on thiocyanate; the higher peroxythiocyanates are thought to be antimicrobial (209).

nide is a low-level, widespread pollutant and present, for example, in inhaled cigarette smoke and in fire atmospheres, particularly of plastics. High levels of thiocyanate and cyanide have been noted in the blood of cigarette smokers and of smoke-inhalation victims (214, 215).

The relative importance of the 3-mercaptopyruvate and cysteine sulfinate pathways of cysteine metabolism remains in doubt. Stipanuk (216) concluded from careful studies of the fate of label derived from dietary L-[$^{35}$S]cysteine that, in the rat, the major pathway for cysteine metabolism is the cysteine sulfinate pathway. On the other hand, Krijgsheld et al (217) showed recently that oral administration of both D- and L-cysteine to rats resulted in 55% and 33% recovery of sulfur as sulfate in the urine within 24 hours. The sulfate derived from D-cysteine could not have come from cysteine sulfinate; D-cysteine is not a substrate of cysteine dioxygenase (218). Presumably, D-amino acid oxidase converts D-cysteine to 3-mercaptopyruvate, which can readily yield thiosulfate via transsulfuration; thiosulfate can then react through the thiosulfate cycle to yield sulfate (see Figures 5 and 7). The experiments of Krijgsheld et al (217) also suggest that transamination of 3-mercaptopyruvate in vivo is not very extensive. Thus no increase in taurine levels was noted following administration of D-cysteine; in contrast, L-cysteine administration markedly raised taurine levels (217). Possibly, as with methionine, the $\alpha$-keto acid pathway is more important for the metabolism of the D-isomer of cysteine. Evidently the capacity to metabolize 3-mercaptopyruvate in the rat is very great, so that the limiting step in the 3-mercaptopyruvate pathway would appear to be the transamination of cysteine. Nevertheless, even though the 3-mercaptopyruvate pathway under normal conditions, i.e. L-cysteine breakdown, appears to be quantitatively a minor route, it is of major importance for the transfer of thiolane sulfur, both as a normal metabolic process and as a defense against toxins such as cyanide.

## $\alpha$-KETO ACID ANALOGS OF METHIONINE, CYST(E)INE AND HOMOCYST(E)INE

Waelsch & Borek (219) first prepared $\alpha$-keto-$\gamma$-methiolbutyrate in 1939 by oxidizing D-methionine with kidney slices. $\alpha$-Keto-$\gamma$-methiolbutyrate may be more readily obtained by incubating L-methionine with L-amino acid oxidase and catalase (220). The $\alpha$-keto acid has also been chemically synthesized via hydrolysis of the appropriate azlactone (221). The sodium salt is relatively stable and the $\alpha$-keto acid exhibits typical $\alpha$-keto acid behavior (222). 3-Mercaptopyruvate (the $\alpha$-keto acid analog of cysteine) cannot be made by oxidation of L-cysteine with L-amino acid oxidase, although cysteine is a substrate (192). Oxidation gave rise to a number of products, one

of which was 3-mercaptopyruvate-cysteine disulfide (192). However, if the reaction was carried out in the presence of lactate dehydrogenase and NADH, 3-mercaptolactate was formed in good yield (192). 3-Mercaptopyruvate has been prepared as the ammonium salt by reacting β-chloro- or bromopyruvate with ammonium sulfide (180, 223). 3-Mercaptopyruvate is more reactive than most α-keto acids and readily undergoes aldol condensation particularly at alkaline pH; it is more stable under acidic conditions (192). Kumler & Kun noted that 3-mercaptopyruvate exhibits an anomalous carboxyl $pK_a$ value and infrared spectrum (5, 202, 224). Despite negligible absorbance of aqueous solutions in the region 285–330 nm, it was concluded that 3-mercaptopyruvate exists largely in an enolic form (5, 224). However, 3-mercaptopyruvate was shown recently to exist in solution in equilibrium with a cyclic dithiane (Figure 8; 192). Most likely, this dithiane formation accounts for the anomalous kinetics noted for the reaction of 3-mercaptopyruvate with rat liver glutamine transaminase (78) and with lactate dehydrogenase (225).

The diketo acid analog of cystine, 3-mercaptopyruvate disulfide, has been chemically prepared by oxidation of 3-mercaptopyruvate with iodine (180, 223). The 2,4-dinitrophenylhydrazone of 3-mercaptopyruvate can also be oxidized to the corresponding disulfide (180, 223). However, treatment of 3-mercaptopyruvate disulfide with 2,4-dinitrophenylhydrazine results in a product with only one hydrazone linkage (180). Cysteine is a substrate of L-amino acid oxidase. The initial product is 3-mercaptopyruvate-cysteine mixed disulfide (212, 226–228). There is some evidence that this molecule is also a substrate of L-amino acid oxidase (212, 227). However, Ricci et al (228) presented evidence that 3-mercaptopyruvate-cysteine mixed disulfide cyclizes to a seven-membered dicarboxyl dihydro-dithiazine ring, analogous to the "cystaldimine" structure formed from cystamine (Figure 6).

The α-keto acid analog of homocysteine has not been isolated, although both homocysteine and homocystine are substrates of L-amino acid oxidase (226, 229). Cooper & Meister showed that α-keto-γ-mercaptobutyrate is unstable in solution; however, the corresponding 2,4-

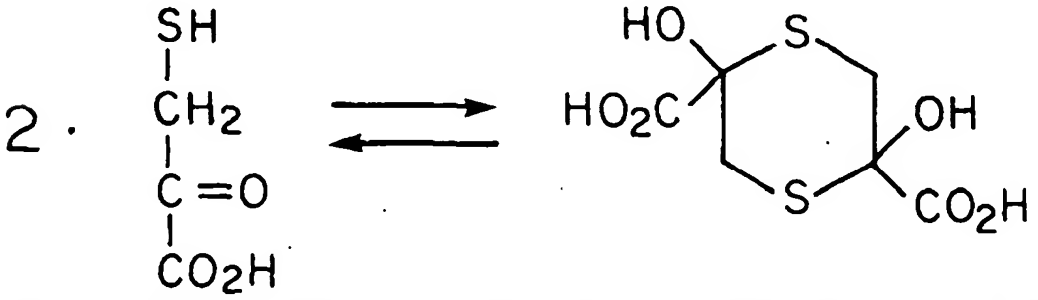


*Figure 8* Equilibrium between 3-mercaptopyruvate and 2,5-dihydroxy-1,4-dithiane-2,5-dicarboxylate.

dinitrophenylhydrazone and its disulfide can be prepared (229). Oxidation of DL-homocysteine with L-amino acid oxidase gives rise to at least seven products, five of which have been tentatively identified, respectively, as α-keto-γ-mercaptobutyrate, the mono and diketo analogs of homocystine, and the mono and diketo analogs of homolanthionine (229). Apparently, some of the imine derived from homocysteine (the initial oxidation product) hydrolyzes to the α-keto acid, but another portion undergoes spontaneous β,γ-elimination of $H_2S$ followed by γ-addition of $RS^-$ giving rise to "keto" homolanthionine derivatives. Similar nonenzymatic β,γ-elimination-γ-addition reactions were previously noted with the imine derived from methionine sulfoximine (230). These nonenzymatic γ-exchange reactions are similar to the enzymatic γ-exchanges catalyzed by cystathionine γ-synthase and methionase (231), except that in these examples the imine nitrogen is part of an enzyme-bound pyridoxal *P*-ketimine. Homolanthionine [$S(CH_2CH_2CHNH_2CO_2H)_2$] is a rare amino acid found to accumulate in methionine-requiring mutants of *E. coli* (232) and in the urine of patients with homocystinuria (233). Presumably homolanthionine arises at least in part via an enzymatic (or nonenzymatic) γ-replacement reaction. α-Hydroxy-γ-mercaptobutyrate-homocysteine mixed disulfide is also present in the urine of individuals with homocystinuria (233, 234). Presumably, homocysteine is transaminated in vivo to the corresponding α-keto acid, which is then reduced to α-hydroxy-γ-mercaptobutyrate. In support of this hypothesis is the recent finding that homocysteine can be transaminated in vitro; the corresponding α-keto acid is also a substrate of lactate dehydrogenase (229).

## CYSTEINE- AND HOMOCYSTEINE-CARBONYL ADDUCTS

It has been known for more than 45 years that cysteine reacts with ketones, such as pyruvate, to yield crystalline hemithioketals (235, 236). In the reaction with reactive aldehydes, such as glyoxylate (237) and pyridoxal *P* (e.g. 238), water is lost and a cyclic thiazolidine is formed. L-Cysteine-α-keto acid hemithioketals can be chromatographed on paper, and can be detected with ninhydrin; they are substrates of L-amino acid oxidase (192). Homocysteine is also known to react with pyridoxal-*P*, presumably to yield a thiazine. Recently, Dewhurst & Griffiths (239) reported that they had crystallized this thiazine and confirmed its structure, but gave no details. Homocysteine-glyoxylate hemithioacetal and homocysteine-pyruvate hemithioketal have recently been prepared (229). Homocysteine-α-keto acid hemithioketals are relatively stable and can also be detected with ninhydrin following paper chromatography (229).

Both cysteine (e.g. 240) and homocysteine (e.g. 241, 242) inhibit pyridoxal-*P* enzymes, presumably by forming cyclic adducts at the active site. Homocysteine appears to inhibit enzymes such as GABA transaminase (241) and glutamate decarboxylase (242), both by competition with substrate and by forming an inhibitor/cofactor complex. High concentrations of cyst(e)ine (54, 243–245) and homocyst(e)ine (54, 246–249) are toxic to the central nervous system. Part of this toxicity may stem from adduct formation with essential carbonyls (e.g. with pyridoxal-*P* enzymes).

Collagen disease often occurs in patients with homocystinura. Jackson (250) reported that homocysteine reacts with formaldehyde and suggested that in homocystinurics, high levels of homocysteine will react with the aldehyde groups of procollagen; such a blockage will impede cross-linking, thus destabilizing the collagen. In support of this theory, homocysteine was shown to react directly with collagen in vitro, destroying the aldimine bridges formed between lysine and allysine (251).

Accelerated arteriosclerosis is a feature of several disorders of sulfur amino acid metabolism (e.g. 252). Several authors have attempted (with varying success) to produce an animal model of this disease by injection of DL-homocysteine lactone (252–256) or L-homocystine (257, 258).[7] The mechanism of arteriosclerosis in this animal model remains unknown but may also be related to S-adduct formation with essential carbonyls.

Many linear addition complexes of glyoxylate and –SH compounds [thioacetals; i.e. R–S–C(OH)$HCO_2H$] are substrates of L-$\alpha$-hydroxy acid oxidase (260). On the other hand, when cyclization occurs with loss of water, the resultant thiazolidine is a substrate of D-amino acid oxidase (261, 262). Hamilton et al (261) suggested that the D-amino acid oxidase-catalyzed conversion of cysteamine + glyoxylate to $\Delta^2$-thiazoline-2-carboxylate, via a thiazolidine intermediate, may be of physiological importance (261). $\Delta^2$-Thiazoline-2-carboxylate has recently been shown to inhibit dopamine $\beta$-hydroxylase (263).

## ROLE OF CYSTEINE IN PIGMENT FORMATION

Glutathione and cysteine are important for the synthesis of several types of pigments (for review see 264, 265). Tyrosine, in the presence of cysteine and tyrosinase (266) or peroxidase (267), gives rise to various cysteinyldopas. [If the oxidation of tyrosine is carried out in the presence of glutathione, glutathionedopas are generated that are enzymatically cleaved to cysteinyl-

[7]Homocysteine thiolactone is readily hydrolyzed to homocysteine in alkali or by pig liver carboxyesterase (259). At high concentrations the lactone readily forms a diketopiperazine (259). Therefore, some caution is needed when using the thiolactone in animal studies (259).

dopas (265)]. Generally, the major product is 5-(S)-cysteinyldopa with smaller amounts of 2-(S)-cysteinyldopa, 6-(S)-cysteinyldopa, 2,5-(S,S)-dicysteinyldopa, 3,5,6-(S,S,S)-tricysteinyldopa, and dihydrobenzothiazines (264–267). Interestingly, 2,5-(S,S)-dicysteinyldopa was first isolated from eyes of the alligator gar, *Lepisosteus spatula* (268). It has been assumed that 5-(S)-cysteinyldopa is produced by the nonenzymatic 1,4-nucleophilic addition of cysteine to dopaquinone (267) (equation 27). However, Nkpa & Chedekel (269) could not obtain evidence for such a mechanism from model reactions and suggested a free radical mechanism involving nucleophilic attack on the semiquinone species (269):

$$\text{Tyr} \xrightarrow{O_2,\ \text{enz}} \text{dopa} \xrightarrow{O_2,\ \text{enz}} (\text{dopaquinone}) \xrightarrow{+\ \text{cys; 1,4-addition}} \text{5-(S)-cysteinyldopa.} \quad 27.$$

Prota et al (270) showed that the 5-(S)-, 2-(S)-, and 2,5-(S,S)-cysteinyldopas are excreted in the urine of patients with melanomas. However, the 5-(S)-isomer was shown recently to be a normal constituent in urine (271).

Generally, three types of pigments are regarded as arising from the oxidation of tyrosine: (*a*) eumalins (black-brown), (*b*) phaeomalins (yellow-reddish brown), and (*c*) trichochromes (yellow-red). The eumalins contain little sulfur and are not derived from cysteinyldopas; the phaeomalins and trichochromes are derived from the oxidation of cysteinyldopas (Equation 28). The structures of several trichochromes, which occur in small quantities in red hair, have been elucidated (265). For a discussion of the occurrence of the three pigments in the various human racial types, see (264).

$$\text{Cysteinyldopa} \xrightarrow{O_2,\ \text{tyrosinase}} \underset{\text{intermediates}}{\text{benzothiazinylalanine}} \longrightarrow \underset{\text{trichochromes.}}{\text{phaeomalins} + } \quad 28.$$

## INBORN ERRORS OF SULFUR AMINO ACID METABOLISM

Sulfituria and 3-mercaptopyruvate-cysteine disulfiduria were cited above. Several other diseases in which sulfur amino acid metabolism is affected either directly or indirectly are known (Table 1; for review see 7, 8, 46, 169, 251, 272–279). There are at least four causes of homocystinuria. Homocystinuria I is caused by a defect in cystathionine $\beta$-synthase; the other types are caused by defects of the remethylation cycle. Two types of cystathionine $\beta$-synthase deficiency are known, a type that responds to $B_6$ treatment and

another that does not. Similarly, $B_6$-responsive and $B_6$-unresponsive forms of $\gamma$-cystathionase deficiency have been described. Note that both methylmalonyl CoA mutase and $N^5$-methyltetrahydrofolate-homocysteine transmethylase require methylcobalamin as a cofactor. Therefore, methylmalonic aciduria is also a feature of homocystinuria types III and IV. Patients with 3-mercaptopyruvate cysteine disulfiduria (169, 195–199), sulfituria (194), homocystinuria (233, 234), and cystathioninuria (280) excrete a large number of unusual sulfur-containing amino acids. In addition to those already mentioned, may be added 5-amino-4-imidazolecarboxamide-5'-S-homocysteinylriboside (AICHR), a previously unknown amino acid found in the urine of homocystinuric patients (233). By 1972, Ohmori et al (234) identified 25 new sulfur amino acids in the urine from various species including eleven from the urine of homocystinuric patients.

Cystinosis is caused by an impairment of cystine transport (e.g. 279; and references quoted therein). Very recent evidence suggests that lysosome function is compromised in this disease (281, 282). Thus, cystinotic fibroblasts can be loaded with cystine by incubation in a medium containing glutathione-cysteine mixed disulfide; on removal of the disulfide from the medium, cysteine is very slow to clear from the lysosomes, compared to

Table 1 Inborn errors affecting sulfur amino acid metabolism in man

| Name | Defect[a] | Number in Figure 2 or 5 | Selected references |
|---|---|---|---|
| Hypermethioninemia | Liver methionine adenosyltransferase ↓[b] | 1 | 276, 279 |
| Homocystinuria (I) | Cystathionine $\beta$-synthase ↓ | 2 | 8, 46, 273, 274, 276–279 |
| Cystathioninuria | $\gamma$-Cystathionase ↓ | 3 | 8, 46, 273, 275, 276, 278, 279 |
| *Cystinosis* | Impairment of cystine transport | | 273, 274, 279, 281, 282 |
| Homocystinuria (II) | $N^5,N^{10}$-Methylenetetrahydrofolate reductase ↓ | 4 | 8, 46, 274, 277, 279 |
| 3-Mercaptopyruvate-cysteine disulfiduria | 3-Mercaptopyruvate sulfurtransferase ↓ | 5 | 8, 169, 276, 279 |
| Sulfituria (sulfocysteinuria) | Sulfite oxidase ↓ | 6 | 273, 275, 279 |
| Homocystinuria (III) | Low $N^5$-methyltetrahydrofolate-homocysteine transmethylase activity because of inability to synthesize cobalamin cofactor | | 46, 277, 279 |
| *Homocystinuria (IV)* | *Defective intestinal $B_{12}$ absorption from gut* leading to low $N^5$-methyltetrahydrofolate-homocysteine transmethylase activity | | 46, 277, 279 |
| Methionine maladsorption syndrome | Inability to absorb methionine from gut | | 276 |

[a] Down-pointing arrow denotes low or absent enzyme activity.
[b] May occur also in cystathioninuria, tyrosinemia, and fructose intolerance.

control fibroblasts or to fibroblasts obtained from heterozygous individuals (281). Similarly, cystinotic leukocytes can be loaded with cystine by exposure to cystine dimethyl ester; again, clearance of cystine from the lysosomes of cystinotic leukocytes was shown to be much slower than in control leukocytes (282).

## L-METHIONINE AND L-CYST(E)INE REQUIREMENT OF CANCER CELLS

A survey of six studies showed that in all cases normal human and rodent cell lines in culture can grow adequately in the presence of homocysteine instead of methionine (283). In contrast, malignant rodent cells and some malignant human cell lines have an absolute requirement for methionine (283, 284). Kreis et al (284) showed that in two human embryonic fibroblast lines (one line that had an absolute requirement for methionine and another that did not) growth was completely retarded by the addition of L-methionase to the medium. Growth was partially restored to the homocysteine-utilizing line, but not to the line with a requirement for methionine, by addition of D-homocystine or L-homocysteine thiolactone (284). The mechanism of rescue is unknown, but the data suggest that "methionine starvation" in vivo may have some therapeutic value (283).

Uren & Lazarus (285) have reviewed the cyst(e)ine requirements of certain malignant cell lines (285). Some cells are susceptible to enzymatic cyst(e)ine depletion in vitro. However, enzyme therapy in vivo has yet to be demonstrated because of rapid clearance of enzyme from the blood (285). Still, the possibility remains that some cysteine-utilizing enzyme(s) or in vivo inhibitors of $\gamma$-cystathionase may be of therapeutic value. Recent work suggests that propargylglycine is active against $\gamma$-cystathionase in rats in vivo (286), but whether this compound or related compounds is of clinical use remains to be seen.

## INDUSTRIAL APPLICATIONS

Soybean protein is a major feed for livestock. It is heralded as a low-cost meat substitute (287) and as an ingredient in milk substitutes in infant formulas (288). However, although the quality of soybean protein is high compared to other vegetable proteins, it is limiting in L-methionine (289). Direct addition of L-methionine is expensive whereas addition of DL-methionine is less so. However, addition of L-methionine or of DL-methionine to foodstuffs results in unappetizing flavors caused by bacterial degradation and release of volatile sulfides (290, 291). Furthermore, despite earlier

reports to the contrary, D-methionine may not be well utilized in man (289).[8] Not surprisingly, researchers are putting a great deal of effort into developing a cheap, palatable methionine analog that can be converted readily to methionine in vivo. One possibility is *N*-acetylmethionine, which has been shown to effectively replace L-methionine in the diet of rats (296), adult humans (289), and one-year-old fasting infants (297). However, the compound that has received most attention is hydroxymethionine analog, or HMA, (DL-$\alpha$-hydroxy-$\gamma$-methiolbutyrate, calcium salt; Monsanto Chemical Co.). HMA is now manufactured in large quantities as a supplement to livestock feed.

In 1932 Block & Jackson reported that the zinc salt of HMA can promote growth (298). Subsequently, the DL-isomer was shown to promote growth in a number of species (47, 299), and recently the growth response to the D- and L-isomers in chicks has been investigated (299). It was found that efficacy in isosulfurous amino acid formulations was in the order L-HMA $<$ DL-HMA $<$ D-HMA $<$ D-MET $\leq$ L-MET (299). Apparently, the D- and L-HMA isomers are converted to $\alpha$-keto-$\gamma$-methiolbutyrate in vivo, by D- and L-$\alpha$-hydroxy acid dehydrogenase, respectively (299). Interestingly, it has long been known that $\alpha$-keto-$\gamma$-methiolbutyrate can replace methionine in the diets of rats (221). Langer showed that in the rat, HMA is converted to $\alpha$-keto-$\gamma$-methiolbutyrate, which is then transaminated to L-methionine (300). Glutamine, and to a lesser extent asparagine, were required for the transamination reaction (300). As discussed above, $\alpha$-keto-$\gamma$-methiolbutyrate is a good substrate of rat liver and kidney glutamine transaminases and of rat liver asparagine transaminase (78, 80).

S-Carboxymethylcysteine (Mucodyne, Berk Pharmaceuticals) is an orally effective mucolytic agent used clinically for the treatment of respiratory disorders (301). Following oral administration of $^{35}$S-carboxymethylcysteine to rats, label is concentrated in mucus-producing organs including the prostate in the male and the cervix in the female (301).



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[8]Earlier results suggested that D-methionine could effectively replace L-methionine in the diet in mice (292), rats (293), and man (294). More recent studies indicate that puppies can also utilize D-methionine (47). However, Zezulka & Calloway (289) were unable to demonstrate efficient utilization of D-methionine in man, even in the presence of choline (to prevent loss of methyl groups) and sulfate (to spare methionine; cf 295).

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